

**REMARKS**

Entry of the foregoing, and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

Applicants are pleased to note that the previous rejections under obviousness-type double patenting and under 35 U.S.C. § 103 are withdrawn.

***Rejections Under 35 U.S.C. § 103***

Claim 1 stands rejected under 35 U.S.C. § 103(a) as purportedly obvious over Southern et al. (WO95/04160, published February 9, 1995) ("Southern") in view of Smith, L. M. (Nature, 1991, 349: 812-813) ("Smith") and Koster (U.S. Patent No. 5,547,834, issued August 20, 1996) ("Koster").

Applicants respectfully traverse the rejection. For a *prima facie* case of obviousness, the following three requirements must be met. First, the prior art relied upon coupled with the knowledge generally available in the art at the time of the invention must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine the reference with another reference. Second, the proposed modification must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. Third, the prior art reference must teach or suggest all the limitations of the claims. The teachings or suggestions as well as the expectation of success must come from the prior art and not from applicant's disclosure. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d

1016, 1023 (Fed. Cir. 1991); and *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

Applicants respectfully submit that the cited references, alone or in combination, do not mean the requirements for a *prima facie* case of obviousness. There is no motivation to modify the teachings of Southern, alone or in view of Smith and Koster for the claimed purpose. Nor is there an expectation that such a modification would lead to the successful methods of characterizing DNA of the present invention.

The presently claimed invention is directed to improved methods of sequencing, particularly based on conventional Sanger chemistry and capillary electrophoresis separation of tagged Sanger ladders. The present methods exploit the advantages of collision cleavable mass tags. The use of these particular mass tags allows multiple sequences to be determined in a single capillary electrophoresis separation, because multiple sets of tags can be used to identify the terminating nucleotides for each of a series of sequencing reactions.

The advantage of collision cleavage is that the cleavage of the tags and subsequent detection can take place in-line, because the cleavage step is virtually instantaneous. In fact, the eluent from the capillary electrophoresis can be sprayed directly into the mass spectrometer where the cleavage step takes place. Using in-line analysis with photocleavable tags, instead as disclosed by Southern, would be problematic after a capillary electrophoresis separation, because the photocleavage step is comparatively slow, creating a technical hurdle for the use of mass tags. The present invention avoids this problem.

The Office has previously argued that it would be obvious for the skilled artisan to turn to Southern et al. which provides an array of oligonucleotide probes that are identified by photocleavable mass tags. However, as Applicants have previously noted, photocleavage is problematic. In fact, the Office has acknowledged that Southern does not disclose the use of Collision Induced Dissociation (CID).

Southern discloses a method of sequencing by hybridization, which does not require electrophoresis, as the sequence of a target is determined simply by determining to which probes, from an array of probes, the target is hybridized (after a ligation step). In fact, Southern discloses the advantages of array-based methods over gel electrophoresis based methods (see page 21, line 28 to page 22, line 19). Thus, the skilled artisan would not turn to Southern, the primary reference, to provide a method of improving electrophoresis based methods, because Southern teaches away from electrophoresis-based methods.

The deficiencies of Southern are not remedied by the other secondary references. Smith relates to the use of capillary electrophoresis and does not provide motivation to combine with the other references or any expectation of success.

New secondary reference Koster, combined with Smith and Southern, does not remedy the deficiencies of Southern. The Office supports the obviousness rejection by referring to a passage in Koster (see column 5, lines 41-67), which is directed to the fact that CID can be used to obtain structural information about molecules under analysis. The Office thus asserts that it would be obvious to combine Koster with the disclosures of Southern, which discloses the use of photo-

cleavable mass tags in a method of sequencing by hybridization and the disclosure of Smith, which is cited as purportedly directed to the use capillary electrophoresis to improve conventional Sanger sequencing with four fluorescent dyes.

When taken as a whole, Koster does not disclose or suggest that CID can be used to detach a cleavable mass tag from a nucleic acid. To set forth a case of *prima facie* obviousness, the reference must be viewed as a whole for what it teaches; "[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965); *see also Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986).

In support of the assertion that the Office is picking and choosing from Koster, Applicants note that Koster makes only a passing reference to CID. In fact, Koster does not suggest that CID can be used to detach a cleavable mass tag from a nucleic acid. When read as whole, Koster actually teaches away from the use of cleavable mass tags altogether, let alone collision cleavable mass tags. To this end, Koster discloses a method of determining the sequence of a nucleic acid that specifically does not use cleavable mass tags. The method in Koster generates a Sanger termination ladder outside the mass spectrometer using conventional terminator chemistry and then determines the sequence of the nucleic acid by measuring the mass of the Sanger Ladder fragments by conventional non-collision based mass analysis.

The mass modifiers set forth in Koster are not designed to be cleaved. Instead, the purpose of the mass modifiers in Koster is to alter the mass of the Sanger ladders generated to give more accurate results and potentially to allow the masses of several ladders to be determined simultaneously by offsetting different sequence ladders from each other (see Koster, column 15, line 27 to column 20, line 51). Moreover, Koster discloses that the advantage to the methods disclosed in Koster is that electrophoresis is not required (see abstract as well as column 8, lines 23-26).

Thus, Koster discloses a method of sequencing that teaches away from the presently claimed method, because Koster proposes using mass spectrometers for direct analysis of Sanger DNA ladders. This method is different from the presently claimed method, which analyzes DNA sequences indirectly through the detection of tags after capillary electrophoresis separation of Sanger DNA ladders. In addition, Koster explicitly states that one of the problems with conventional sequencing is the capillary electrophoresis step. The capillary electrophoresis step is crucial to the presently claimed invention. Finally, Koster teaches away from the present method by providing a method of analyzing DNA that is dependent on mass modifiers that are not cleaved. When taken as a whole, Koster does not teach that CID can be used to cleave a tag, and teaches away from the present invention.

In light of the above, the skilled artisan would not be motivated to combine Koster with the other cited references, or have any expectation of success upon doing so.

Claims 2-18 and 20-26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Southern et al. in view of Ness *et al.*, Alberts (Molecular Biology of

the Cell, 1994, page 298) ("Ness"); Smith, L.M. (Nature, 1991, 349: 812-813) and Koster. Claims 2-18 and 20-26, whether dependent on claim 1 or independent, also requires a step of electrophoresis as in claim 1. In light of the above comments regarding claim 1, Applicants submit that Southern, in view of Ness, Alberts, Smith, and Koster, still bears the same deficiencies as in the above rejection of claim 1, which are not remedied by the addition of secondary references Alberts and Ness. Thus, Applicants request that this rejection be withdrawn.

Claim 27 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Southern *et al.* in view of Ness *et al.*, Smith, and Koster. Claim 27 also requires a step of electrophoresis. In light of the above, Applicants submit that Southern, in view of Ness, Smith, and Koster, still bears the same deficiencies as in the above rejection of claim 1, which are not remedied by the addition of secondary reference Ness. Thus, Applicants request that this rejection be withdrawn.

Claim 28 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Southern *et al.* in view of Ness *et al.*, and Koster. Claim 28 also requires a step of electrophoresis. In light of the above comments, Applicants submit that Southern, in view of Ness, Smith, and Koster, still bears the same deficiencies as in the above rejection of claim 1, which are not remedied by the addition of secondary reference Ness. Thus, Applicants request that this rejection be withdrawn.

***Judicially created doctrine of obviousness-type double patenting***

Claims 1-18, 20-24 and 27-28 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 63-

80 of U.S. Patent No. 10/221,666. Applicants respectfully request that this rejection be held in abeyance until allowable subject matter is indicated.

**CONCLUSION**

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

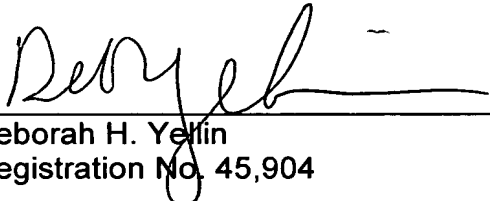
In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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